

3. Applicants note that claims 28, 33-38, and 43-45 are withdrawn to the extent they read on BMP-2, BMP-5, BMP-6, and 60A. Applicants respectfully point out, however, that pursuant to MPEP 803.02, “should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended.” Accordingly, if the prior art rejections are withdrawn, these claims should be considered throughout their scope.

4. Claims 28 and 37-38 are objected to as reciting an improper Markush group. The Office Action cites MPEP 803.02 in support of this objection. Applicants wish to point out that this section also states that “This subsection deals with Markush-type generic claims which include a plurality of alternatively usable substances or members. ... A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated or diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. § 103 with respect to the other member(s). In applications containing claims of that nature, the examiner may require a *provisional* election of a single species prior to examination on the merits. The *provisional* election will be given effect in the even that the Markush-type claim should not be found allowable. ...

“...[S]hould no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended.” (emphasis added)

Accordingly, Applicants submit that no amendment of the claim is required under MPEP 803.02 at this time, and that if the prior art rejections are withdrawn, these claims should be considered throughout their scope.

Moreover, the elements of the Markush group of claim 28 are OP-1, BMP-2, BMP-5, BMP-6 and 60A polypeptide. These morphogens have a common functionality since they induce dendritic outgrowth and synapse formation in hippocampal neurons. In addition, the claimed morphogens share common structural features since they all have at least 89% amino acid sequence similarity in the C-terminal seven-cysteine domain. See Figure 1, and compare the sequence similarity of the proteins claimed in the Markush group. Consequently, Applicants respectfully submit that the morphogens claimed in the Markush group do share common

structural features as well as functional characteristics, and this objection should therefore be withdrawn.

5-6. Claims 28 and 37-38 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is not adequately described in the specification. This ground of rejection is respectfully traversed.

The Examiner has argued that the particular morphogens recited in the claims, namely OP-1, BMP-2, BMP-5, BMP-6 and 60A protein, do not satisfy the written description requirement since the particular morphogens recited in the claims are not adequately described.

In response, applicants note that the claimed morphogens are known and well characterized in the art. See, for instance, the references listed on pages 1, 2, 17 and 18 of the specification. See, also, WO 94/03200, cited in the Office Action, which contains a detailed description of the morphogens claimed in this application. Accordingly, there is no need to describe these morphogens in detail in the instant specification since they are well known and fully described in the literature. "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." Federal Register, Vol. 66, No. 4, p. 1106 ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, 'Written Description' Requirement").

Moreover, the present claims are not directed to compositions per se, but rather to methods for treating damaged hippocampal tissue, and methods for restoring a function of a damaged hippocampal tissue, using these morphogens. The cases cited by the Examiner apply to composition claims, not method claims, and are not pertinent to the facts of this case. Reconsideration and withdrawal of this rejection are respectfully requested.

7. Claims 28-32 and 37-42 have also been rejected under 35 U.S.C. 112, first paragraph, since the specification allegedly does not enable one skilled in the art to make and use the claimed invention. In particular, the Examiner states that the present claims, drawn to methods for treating damaged hippocampal tissue, or for restoring the function of damaged hippocampal tissue, are not reasonably supported by the specification. This ground of rejection is respectfully traversed.

The Examiner acknowledges that the specification is enabling for accelerating dendritic outgrowth of hippocampal neurons in culture in the presence of OP-1. However, the Examiner questions whether the application supports morphogens other than OP-1, the operability of the method to cells which are not maintained in culture (i.e., cells *in vivo*), and the operability of the invention in a variety of hypothetical circumstances. This ground of rejection is traversed.

Claim 28 has now been amended to recite a method for enhancing the formation and development of dendrites and synapses in hippocampal cells. Claim 37 has also been amended to recite a method for reducing memory dysfunction associated with damaged hippocampal tissue.

Although the Examiner states that the specification is not enabling for the morphogens BMP-2, BMP-5, BMP-6 and 60A protein, based on a lack of exemplification, Applicants maintain that there is no requirement that an example must be provided for each of the claimed species. Such a requirement would be unduly burdensome on Applicants, and in any event, actual examples are not legally required in order to establish patentability. Moreover, and contrary to the Examiner's assertions regarding a lack of common core structure of amino acids comprising the claimed morphogens, Figure 1 shows that all of the claimed morphogens have at least 89% sequence similarity to human OP-1 in the seven-cysteine domain. This provides the requisite structural similarity required to satisfy the enablement requirement.

The Examiner states that the references cited in the Office Action establish the unpredictability of the invention in view of the fact that the morphogens have uses other than the uses claimed herein, such as bone growth enhancers. Proof of other uses for these biologically active proteins does not, however, in any way serve as evidence that one skilled in the art would question their effectiveness for treating hippocampal cells in the manner claimed by applicants.

Moreover, Applicants' specification is presumed correct, since it is a document which is submitted under oath. Unless the Examiner has provided credible evidence that the specification is incorrect, the specification must be accepted as correct. In this instance, the Examiner has supplied a reference indicating that the regeneration of neurons in the CNS is a difficult scientific problem. However, WO 94/03200 and WO 95/05846, both cited in the Office Action, indicate that certain aspects of this problem have been addressed with some success. The references supplied by the Examiner do not establish that the present invention is inoperable since they do

not contradict any of the statements made, or the examples provided, by Applicants in the specification. The references and merely constitute a general scientific disclosure which in any event is not encompassed by the instant claims. However, the references are effective in demonstrating, in a general sense, that the problem addressed by Applicants may be a difficult one, and this is fully consistent with Applicants' contention that the invention is not obvious in view of the known state of the prior art.

Applicants disagree with the Examiner's assertion that the utility of the present morphogens should be limited to an *in vitro* model. Simply because certain experimental work has been conducted *in vitro* for the sake of expense and convenience, does not mean that this limitation should be part of the claims. There is no credible evidence of record to support the assertion that applicants' *in vitro* model would not be an accurate predictor of *in vivo* activity. The reference cited by the Examiner in support of the idea that *in vivo* processes are more complex than *in vitro* process is acknowledged. However, Applicants have developed a complex model in order to simulate *in vivo* activity specifically for the purpose of taking these complexities into account. There is no basis for requiring that the claims should be limited to *in vitro* activity.

Finally, the specification fully supports the use of the claimed morphogens to reduce memory dysfunction associated with hippocampal tissue damage, and for enhancing the development and formation of dendrites and synapses in hippocampal cells. See, for instance, pages 48-55 (memory function), and pages 59-61 (enhancement of dendrite activity). Although the Examiner has questioned the applicability of the invention to hippocampal cells which have been damaged beyond repair, the specification makes no such claim. If a hippocampal cell has indeed been damaged beyond repair, then it *ipso facto* cannot be restored to activity and this state would be recognized by one of skill in the art. However, if it has been damaged and can be restored, the claims (claim 28 et seq.) state that such restoration can be accelerated. It is not necessary to specifically recite in the claims that the hippocampal cells have not been damaged beyond repair since this would be understood by one of skill in the art as an inoperative embodiment. MPEP 2164.08(b); *Atlas Powder v. E.I. du Pont de Nemours*, 224 USPQ 409, 414 (Fed. Cir. 1984). Reconsideration and withdrawal of this rejection are respectfully requested.

8-10. Claim 28-32 and 37-42 also stand rejected under 35 U.S.C. 102 as being anticipated by Reuger et al., WO 94/03200, or Wang et al., WO 95/05846. Applicants respectfully traverse this rejection.

The Reuger et al. reference relates to methods for enhancing the survival of neural cells in mammals by treating such cells with a morphogen. However, this reference does not disclose the use of the disclosed morphogens for treating brain tissue to restore memory function. One of ordinary skill in the art could have no reasonable expectation that a treatment method which is effective for enhancing neural cell survival would also be useful for restoring memory function – enhancing survival would only be expected to maintain, not *restore*, memory, by inhibiting further loss of neuronal cells.

Similarly, the Wang et al. reference discloses the use of bone morphogenic protein to induce the growth of neural cells. This reference also fails to disclose the use of morphogens to treat brain cells or brain tissue, or to restore memory function. The idea that such treatment would inherently result in dendritic outgrowth or synapse formation is purely speculative and without support in either reference. “The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.” MPEP 2112. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Date: February 21, 2002

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Respectfully Submitted,



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